REMARKS

By the present amendment, the enclosed Substitute Sheets replace pages 1 through 3 of the Sequence Listing.

The amendments to the written description are fully supported by the application, as filed. Specifically, support for the amendments adding Asp as one of the possibilities for X_3 may be found in the Sequence Listings filed in the applications to which the present application claims priority. These applications are Application Serial Nos. 09/641,587, 09/492,935 and 09/378,567, all pending, and all incorporated by reference into the present invention. In the Sequence Listings filed in 09/492,935 and 09/378,567, SEQ ID NO.: 1 is the native sequence of human TGFα. It can be seen from the SEQ ID NO.: 1 that the amino acid in position #7 is Asp. Therefore, inclusion of Asp as an option for X_3 is supported. Support for the amendment to the specification in formula IV, amending Gln to Asn is also supported by SEQ ID NO.: 1. In SEQ ID NO.: 1, it can be seen that the amino acid in position #6 is Asn. Therefore this amendment has been made to the specification. Similarly, the specification has been amended where it is stated, "wherein T is the native sequence of human TGFα (SEQ ID NO.:1) from amino acid #8 (Cys) to amino acid #44 (Cys)..." However, as can be seen in SEQ ID NO.: 1, in the native sequence of human TGFα amino acid #44 is not Cys, but Glu. The Cys that was referred to is in position #43. Therefore amendment of the position number has been made to the specification to correctly identify the Cys residue. Any other amendments to the written description have been made for clarification. These amendments are the addition of the word "or" between the values of - NH_2 and R_3 - X_3 for R_1, the clarification of X_1 as X_{1a}, X_{1b} or X_{1c}, the addition of sequence identification numbers and the correction of typographical errors. None of the amendments to the written description add any new matter.

CONCLUSION

This Amendment is submitted in order to clarify the invention. No new matter has been added. The new claims are supported by the specification and claims, as originally filed, as set forth above.

In view of the foregoing, Applicants respectfully submit that the claims are in condition for allowance. No fee is deemed necessary in connection with the filing of this response. However, if any fee is deemed necessary, the Commissioner is authorized to charge (or apply any credits to) Deposit Account No.: 50-1355. The Examiner is invited to contact Applicant's undersigned representative if there are any questions related to this matter.

Respectfully submitted,

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EXHIBIT A
VERSION WITH MARKINGS TO SHOW CHANGES

In the Specification:

Please amend the specification as follows:

[0058] In one embodiment the TGF-α polypeptide, related polypeptide, mimetic or functional fragment is a TGF-α polypeptide as set forth in SEQ ID NO:1, SEQ ID NO:3, or a TGFα mimetic selected from the group consisting of formula I, formula II, formula III, formula IV, or formula V, wherein formula I is:

R_1- T - R_2 (I)

wherein R_1 is $-NH_2$, or R_1 is R_3 - X_3 , wherein R_3 is a polyethylene glycol (PEG) attached to the free NH_2 moiety of X_3 (wherein X_3 is Lys [or Arg] or Asp) and having a molecular weight of PEG of from about 2000 daltons to about 10,000 daltons, or one or more of the following seven amino acids from formula [VI] IV, including either L (natural) or D chiral orientations:

$-NH_2$-X_{1a} -X_{1a}- Ser - His - Phe - [Gln] Asn - X_3- (SEQ ID NO: 7) (IV)

wherein [X_1] X_{1a} is independently Val, Gly or Ala and X_3 is Lys [or Arg] or Asp; wherein T is the native sequence of human TGFα (SEQ ID NO. 1) from amino acid residue no. 8 (Cys) to amino acid residue no. [44] 43 (Cys) consisting of native L amino acids; and wherein R_2 is -COOH or one of more of the following seven amino acids, including either L (natural) or D chiral orientations, from formula V:

-X_4- His - X_{1c}- X_4- X_5- X_6- X_{1c}- (SEQ ID NO: 5) (V)

wherein X_4 is Glu or Asp, wherein X_5 is Leu or Ile, wherein X_6 is Asp or Glu, and wherein [X_1] X_{1c} is independently Val, Gly, or Ala.

[0059] The invention provides a peptide having TGF-α biological activity, comprising at least an 11-membered peptide compound of formula II [(SEQ ID NO:4)]:

$-NH_2$- X_{1a}-Cys-His-Ser-X_{1b}-X_2-X_{1a}-X_{1b}-X_{1a}-X_3-Cys COOH (SEQ ID NO:4) (II)

wherein [X_1 is] X_{1a}, and X_{1b} are independently Val, Gly, or Ala, wherein X_2 is Tyr or Phe, wherein X_3 is Arg or Lys, and wherein the two Cys moieties form a disulfide bond to create an

11-amino-acid functional peptide having a 10 member loop structure. In addition, at least one or more of the following amino acids of formula III [(SEQ ID NO:5)] may be added to the C terminus Cys moiety of formula [I] II [(SEQ ID NO:4)]:

$$- X_4 - His - X_{1c} - X_4 - X_5 - X_6 - X_{1c}$$ (SEQ ID NO: 5) (III)

wherein X_4 is Glu or Asp, wherein X_5 is Leu or Ile, [and] wherein X_6 is Asp or Glu and wherein X_{1c} is Val, Gly or Ala. Preferably, X_{1a} is Val, X_{1b} is Gly and X_{1c} is Ala thereby producing an 11, 12, 13, 14, 15, 16, 17 or 18 amino acid peptide. Preferably, X_2 is Tyr, and X_3 is Arg. Accordingly, in one embodiment the functional peptide of the invention has a sequence: NH_2-X_{1a}-Cys-His-Ser-X_{1b}-X_2-X_{1a}-X_{1b}-X_{1a}-X_3–Cys-X_4-His-X_{1c}-X_4-X_5-X_6-X_{1c}–COOH (SEQ ID NO:6)

[0060] SEQ ID NO: 6 forms a 10 member loop structure with a 7 member tail that can be varied in length. In addition, SEQ ID NO: 6 can form dimmers comprising, for example, a 34-mer peptide. Accordingly, the functional peptide can be from about 10 to 18 amino acids in length (*e.g.* 10, 11, 12, 13, 14, 15, 16, 17, or 18 amino acids) wherein X_{1a} is Val, X_{1b} is Gly, X_{1c} is Ala and X_4 is [Gly] Glu and may also comprise hetero- or homo-dimers of various TGF-α peptides described herein. Such dimers may have greater or reduced activities as compared to monomers.

[0061] The invention further provides an active TGF-α57 polypeptide (SEQ ID NO:3), wherein TGF-α57 is a 57 amino acid polypeptide having the formula VI:

Ser - Leu – Ser – Leu – Pro – Ala – Met – Human TGFα (SEQ ID NO: 3) (VI)

Wherein human TGFα is a 50 amino acid polypeptide having a sequence as set forth in SEQ ID NO:1.

[0151] The invention further provides a bifunctional compound that acts as a TGFα mimetic, comprising a compound of formula III:

Loop peptide N-terminus-linker-cyclic $C_4H_8N_2$- linker- Loop peptide N-terminus (VII)

Wherein the linker moiety is designed to link the N-terminus of the Loop peptide to a nitrogen atom of the ring $C_4H_8N_2$ and wherein the "loop peptide" comprises at least an 11-membered peptide compound of formula II:

NH_2- X_{1a}-Cys-His-Ser-X_{1b}-X_2-X_{1a}-X_{1b}-X_{1a}-X_3-Cys COOH (SEQ ID NO:4) (II)

wherein $X_{1a,}$ and X_{1b} are independently Val, Gly, or Ala; X_2 is Tyr or Phe; X_3 is Arg or Lys; and the two Cys moieties are linked via a disulfide bond to form an at least 11-amino acid functional peptide having TGF-α activity. Preferably, at least one or more of the following amino acids are added to the C terminus Cys moiety from formula III, below:

- X_4 - His - X_{1c} - X_4 - X_5 - X_6 - X_{1c} (SEQ ID NO: 5) (III)

wherein X_4 is Glu or Asp, wherein X_5 is Leu or Ile, [and] wherein X_6 is Asp or Glu and wherein X_{1c} is Val, Gly or Ala. Preferably, X_{1a} is Val, X_{1b} is Gly and X_{1c} is Ala. Preferably the linker group is independently selected from the group consisting of substituted or unsubstituted C_{1-6} alkoxy, xylenyl, wherein the substitutions are selected from the group consisting of: oxo, epoxyl, hydroxyl, chloryl, bromyl, fluoryl, and amino. Preferably, X_2 is Tyr, and X_3 is Arg. Most preferably, the functional peptide is 18 amino acids in length wherein X_{1a} is Val, X_{1b} is Gly, X_{1c} is Ala and X_4 is [Gly] Glu.